REMARKS

Claims 14-16, 18-20, and 22-31 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Rejection based on 35 U.S.C. 112, first paragraph. Claims 14-16 and 22-29 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action alleges that while the specification is enabled for a method of preparing a composition comprising the therapeutic agents set forth in claim 18, a complexing agent set forth in claim 20, and a polymer that is cyclodextrin, the specification does not reasonably provide enablement for a method of preparing a compositions comprising the step of: combining a therapeutic agent, a polymer having host and/or guest functionality, and a complexing agent to form the composition.

Applicants respectfully disagree and submit that the specification does in fact provide enablement for the composition of the pending claims. Section 2164.04 of the MPEP states that "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.... As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370." Applicants submit that the Examiner has met not the burden to provide basis for a rejection for lack of enablement.

Applicants respectfully refer the Examiner to example 30, wherein compositions of the invention were prepared by mixing an equal volume of β-cyclodextrin(cystamine)-DMS copolymer (polymer) with DNA (therapeutic agent). The same volume of GALA-Ad

(complexing agent) was then added to provide a composition of the invention. Applicants also refer the Examiner to example 42, wherein oligo (therapeutic agent) was complexed with β-cyclodextrin(cystamine)-DMS copolymer (polymer), and after five minutes, adamantane-PEG-fluorescein (complexing agent) was added to provide the composition. Additionally, Applicants refer the Examiner to the specification (paragraph 146) where general procedures for the preparation of compositions are described, wherein "[t]he inclusion complex may be prepared by any suitable means known in the art. For example, the inclusion complex may be formed by simply contacting, mixing, or dispersing the particulate composite and the complexing agent. For example, the particulate composite and the complexing agent may be mixed in a solvent in which both are soluble, in which the particulate composite or the complexing agent is soluble but the other is dispersed, or in a solvent which disperses the particulate composite and the complexing agent but solubilizes the inclusion complex. Preferably, the inclusion complex is formed by adding the complexing agent to the particulate composite in the same vessel as used to mix the polymer and the therapeutic agent to form the inclusion complex." Applicants assert that given that the experimental procedures used for preparing a composition of the pending claims are simple and routine, a person of skill in the art would certainly be able to successfully prepare a composition comprising a polymer having host and/or guest functionality, a complexing agent, and a therapeutic agent from the information provided in the specification and examples.

With regard to the therapeutic agent of the composition, Applicants maintain that the term "therapeutic agent" was well known in the art at the time. Additionally, the specification (paragraph 110) refers to the Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th Edition, 2001, Merck and Co., Inc., Whitehouse Station, N.J. for examples of therapeutic agents known in the art. Applicants submit that the identity of the specific therapeutic agent used to practice the invention is not important, since the composition set forth in the pending claims is intended as a vehicle to deliver a therapeutic agent to a mammal in recognized need of the therapeutic. The nature of the therapeutic agent is relevant only to the disease or condition that is to be treated, and requires no specialized interactions with the other components of the claimed compositions.

Regarding the polymer having host and/or guest functionality, Applicants submit that the field of host-guest interactions was well developed at the time of filing (see Exhibit A; Cram, D.

J. "The Design of Molecular Hosts, Guests, and Their Complexes" *Science*, **1988**, *240*, 760-767.). Additionally, Applicants refer the Examiner to paragraph 105 of the specification, which states that "[o]ther examples of suitable "hosts" which may be employed with the polymer include, but are not limited to, cavitands, crown ethers, cryptands, cucurbiturils, calixarenes, speherands, and the like. Polymers of these other hosts may be prepared in the same way as described above for the cyclodextrin-containing polymers. Polymers of these other hosts may be derivatized through a functional group such as a hydroxyl group to attach a leaving group such as iodide, tosylate, etc. and reacted with a suitable comonomer A displacing the leaving group and forming the host copolymer. Alternatively, the host may contain or be derivatized to contain a functional group such as an amine or carboxyl group allowing the host to undergo a condensation reaction with a comonomer A to form the host copolymer." Applicants assert that the specification has provided suitable guidance for one of skill in the art to prepare a polymer containing host functionality. Guest functional polymers are also described in the specification (paragraph 106), wherein "typically the guest functionality will be present on a side chain or end-group... Examples of inclusion functionality which may be incorporated into the polymer include those known in the art such as, but not limited to, adamantane, diadamantane, naphthalene, and cholesterol." Applicants assert that the derivatization of polymers to include pendant functionality was well known in the art at the time, and therefore a person of skill in the art would have been able to prepare a guest-functional polymer of the pending claims without undue experimentation. Furthermore, Applicants assert that the Examiner has not provided evidence or reasoning which is inconsistent with the contested statement.

Concerning the complexing agent, Applicants refer the Examiner to paragraph 112, wherein a complexing agent is described as "a compound having host or guest functionality that is capable of forming an inclusion complex with a polymer in the particulate composite having the corresponding guest or host functionality.... The complexing agent also contains a functional group which adds a beneficial property to the composition of the invention. This functional group may be, for example, a ligand, a hydrophilic or hydrophobic group, an additional therapeutic agent, etc." Applicants also respectfully refer the Examiner to paragraph 134, wherein the specification states that "[a] functionalized guest complexing agent may be prepared by any means known in the art. See Amiel et al., *Int. J. Polymer Analysis & Characterization*, Vol. 1, 289-300 (1995); Amiel et al., *Journal of Inclusion Phenomena and*

Molecular Recognition in Chemistry 25, 61-67 (1996); Sandier et al., *Langmuir*, 16, 1634-1642 (2000)." Applicants assert that one of skill in the art would be able to prepare a wide variety of functionalized complexing agents encompassed by the pending claims without undue experimentation in light of the information provided in the specification, examples, and references.

The Office Action states that the "amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles." Applicants respectfully point out to the Examiner that the field of host-guest chemistry was well developed and the characteristics associated with molecules capable of host-guest interactions were well known in the art at the time, thereby establishing a high level of predictability in the art. Applicants further assert that preparing a composition as set forth in the pending claims, e.g., mixing a polymer having host and/or guest functionality, a therapeutic agent, and a complexing agent, does not involve chemical reactions at all, but rather involves merely mixing the three components. Also, Applicants note the Examiner's statement regarding a statement that is "on its face, contrary to generally accepted scientific principles." Applicants are unclear as to the meaning of this statement and respectfully request that the Examiner clarify what aspect of the composition is "contrary to generally accepted scientific principles". Additionally, Applicants note that on page 4 of the Office Action, the Examiner states that "the specification does not offer any guidance on how one of ordinary skill would go about practicing the invention for *recovery* of every claimed therapeutic agent, a polymer having host and/or guest functionality, and complexing agent." (emphasis added). Applicants are unclear as to the meaning of "recovery" in this passage and respectfully request clarification from the Examiner.

For the reasons presented above, Applicants maintain that the specification fully enables the scope of the pending claims given the highly developed state of host-guest chemistry at the time. One of skill in the art could readily prepare a composition as set forth in the pending claims without undue experimentation. Accordingly, Applicants submit that claims 14-16, and

22-29 fully comply with 35 U.S.C. 112, first paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection based on 35 U.S.C. 112, first paragraph. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action states that the specification does no more than describe the desired function of the compound called for, that is, it does not clearly set forth the structure of the desired compounds. Moreover, the Office Action states that the claimed "functional group" contains almost no information by which a person of skill in the art would understand that the inventors possessed the claimed invention. Applicants respectfully refer the Examiner to paragraph 114, wherein examples of suitable functional groups include functional groups that are added in order to enhance some biological function of the composition, i.e., enhance the ability of the composition to localize to a particular tissue of the body, or impart stabilization under biological conditions. This type of functional group includes, but is not limited to ligands, nuclear localization signals, endosomal release peptides, endosomal release polymers, membrane permeabilization agents, or mixtures thereof. The term "functional group" also includes classical functional groups in organic chemistry and may be as simple as a hydroxyl or amine functionality. There are several specific functional groups listed in the examples section of the specification, including an amine (example 23), lactose (example 25), fluorescein (example 28), transferrin (example 55), and galactose (example 59). Applicants submit that the specification has described every element of the claimed invention in sufficient detail so one of skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection based on 35 U.S.C. 103 (a). Claims 14, 18-20, and 22-31 are rejected as being unpatentable over U.S. Patent 5,691,316 (Agrawal). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Claims 14, 18-20, and 22-31, as amended, are directed to a method of preparing a composition, comprising combining a therapeutic agent, a polymer having host and/or guest functionality, and a complexing agent to form the composition, wherein said polymer and said complexing agent form an inclusion complex, and said therapeutic agent, polymer, and complexing agent are separate molecules. The amendment stating that these elements are separate molecules does not exclude the possibility that additional therapeutic agents might be covalently attached to the polymer and/or the complexing agent, but only clarifies that there is at least one discrete therapeutic agent in the composition that is covalently linked to neither the polymer or the complexing agent. Further, the amendment does not exclude the possibility that the therapeutic agent might form an inclusion complex with the polymer and/or the complexing agent, but only excludes covalent attachment.

Agrawal describes "a composition comprising adamantane which is *covalently* linked to an oligonucleotide phosphorothiolate or oligonucleotide phosphodiester and noncovalently complexed with *a* cyclodextrin" (emphasis added). While the use of a therapeutic agent, an adamantane, and cyclodextrin are contemplated, Agrawal provides no suggestion or motivation for one of skill in the art to prepare a composition comprising a therapeutic agent that is a *separate molecule* from an inclusion complex comprising a complexing agent and a *polymer* having host and/or guest functionality.

Furthermore, Agrawal describes experiments directed to determining whether linkage of the cyclodextrin-associated oligonucleotide to adamantane had an effect on their uptake into cells (column 9, line 29). Cells were treated for varying amounts of time with fluorescently labeled

oligonucleotide, fluorescently labeled cyclodextrin associated nucleotide, or fluorescently labeled covalently-linked adamantane/oligonucleotide. In the presence of cyclodextrin, the increase is much more dramatic, with the increase being the greatest with adamantane-linked oligonucleotide. Thus, covalent linkage of oligonucleotides to adamantane enhances the cellular uptake of cyclodextrin-associated oligonucleotides. Given that Agrawal teaches that superior results are a consequence of a *covalent linkage* between the adamantane and the oligonucleotide in comparison to a noncovalent association of cyclodextrin and oligonucleotide, there would have been no motivation in using a therapeutic agent that is a *separate molecule* from the adamantane and cyclodextrin. Additionally, there would be no motivation for the inclusion of adamantane in the composition at all if it were not covalently linked to the therapeutic agent, as the claims require, since functionally the composition would be the same as a composition comprising only the cyclodextrin and therapeutic agent.

Finally, since Agrawal does not teach a composition comprising a therapeutic agent that is a separate molecule from an inclusion complex comprising a complexing agent and a polymer having host and/or guest functionality, therefore Applicants submit that Agrawal does not teach all of the elements of the claim.

For the reasons set forth above, Applicants submit that none of the criteria for establishing a *prima facie* case of obviousness have been satisfied. Accordingly, it is believed that the pending claims satisfy the requirements of U.S.C. 103(a). Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection based on 35 U.S.C. 103 (a). Claims 15 and 16 are rejected as being unpatentable over U.S. Patent 5,691,316 (Agrawal). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Claims 15 and 16 are directed to a method of preparing a composition comprising combining a therapeutic agent, a polymer having host and/or guest functionality, and a complexing agent to form the composition, wherein said polymer and said complexing agent form an inclusion complex and said complexing agent, polymer, and therapeutic agent are combined in a particular order to form the composition.

For the reasons set forth above, Applicants submit that none of the criteria for establishing a *prima facie* case of obviousness have been satisfied. Accordingly, it is believed that the pending claims satisfy the requirements of U.S.C. 103(a). Reconsideration and withdrawal of these rejections are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

David P. Halstead
Reg. No. 44,735

Date: May 28, 2004

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050